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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,092	08/26/2002	Marcus Keep	30-200P	1549

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EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,092	KEEP ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/5/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

REASSIGNMENT AFFECTING APPLICATION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1654.

STATUS OF THE APPLICATION AND CLAIMS

2. Claims 1-12 are pending in the application. The allowance of claims 1-12 is vacated in view of the new ground of rejection as set forth below.

CLAIMS REJECTION-35 U.S.C. § 102(b)

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-, 2, 4 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaswan (U.S. Patent No. 4,649,047).

The reference of Kaswan '047 patent discloses a pharmaceutical composition comprising cyclosporin such as cyclosporin A (CsA) in a concentration of 0.1 to 20 wt% of cyclosporin dissolved in medically suitable excipients, preferably dimethyl sulfoxide (DMSO) administered topically to the eyes i.e., intra-ocular administration (See e.g., abstract; col. 6, lines 21 to 60; Example 2; claims 3, 4, 7, 8 and 13-16) as directed to

claims 1, 2, 4 and 6. Thus, in the absence of evidence or specific structural limitations, the claimed pharmaceutical composition comprising a cyclosporin dissolved in DMSO wherein the cyclosporin is CsA and methods of administering said composition thereof as taught by the reference anticipates claims 1, 2, 4 and 6 as drafted.

4. Claims 1-, 2, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Elzinga et al (Transplantation, Vol. 47, No. 2, pp. 394-395, February 1989).

The reference of Elzinga et al discloses a pharmaceutical composition comprising cyclosporin such as cyclosporin A (CsA) dissolved in DMSO at a concentration of 15 mg/ml and administered by gavages to the animal pairs at a dosage of 15 mg/kg body weight orally (See e.g., page 394) as directed to claims 1, 2 and 6. Thus; in the absence of evidence or specific structural limitations, the claimed pharmaceutical composition comprising a cyclosporin dissolved in DMSO wherein the cyclosporin is CsA and methods of administering said composition thereof as taught by the reference anticipates claims 1, 2, and 6 as drafted.

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaswan (U.S. Patent No. 4,649,047) taken with Elzinga et al (Transplantation, Vol. 47, No. 2, pp. 394-395, February 1989), Broadwell et al (Science, Vol. 217, No. 4555, pp. 164-166, July 9, 1982) and Elias (U.S. Patent No. 5,807,820).

The reference of Kaswan '047 patent as discussed above discloses a pharmaceutical composition comprising cyclosporin such as cyclosporin A (CsA) in a concentration of 0.1 to 20 wt% of cyclosporin dissolved in medically suitable excipients, preferably dimethyl sulfoxide (DMSO) administered topically to the ayes i.e., intra-ocular administration (See e.g., abstract; col. 6, lines 21 to 60; Example 2; claims 3, 4, 7, 8 and 13-16) as directed to claims 1, 2, 4 and 6.

The reference of Kaswan differs from claims 3, 5 and 7-12 in failing to teach a) methods for administering said cyclosporin and DMSO solution by injection into the cerebrospinal fluid, [illegible] intravestibular, into or adjacent to the brain or spinal

cord, or intravenous, intra-arterial, intraparenchymal spaces, or orally, rectally, vaginally, urethrally, bladder cisternally, nasally, intra and peri-ocullary or dermally to a patient, b) use of an article of manufacture comprising packaging material and pharmaceutical agent wherein said pharmaceutical agent comprises DMSO and cyclosporin formulation thereof, c) a method for treating Alzheimer's disease, Parkinson's disease, sclerosis, HIV neuropathy, Guillain-Barre syndrome, neuronal transplantation, neural xenotransplantation, stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity of vestibulocochlear structures and retinal detachment, and d) a method for inducing systemic immunosuppression in patients with transplantation and autoimmune disease. However, the secondary reference of Elzinga et al compares the effect of DMSO with that of the conventional olive oil vehicle on the absorption of cyclosporin following oral administration in rats. The reference states that following oral administration of CsA solution, the absorption of CsA is highly variable and incomplete, ranging from 4% to 26% of the administered dosage in one study in renal transplant recipients. Nevertheless, DMSO is an excellent organic solvent that readily penetrates most tissue membranes, acting as a "carrier" for many solutes, including various drugs. Thus, the reference clearly shows that DMSO penetrates most biological membranes with ease, and has been used as an effective carrier of drugs and other solutes and considered to be safe. The reference of Elzinga concludes by stating that the increased bioavailability of CsA following administration in DMSO is due to enhanced gastrointestinal absorption, although other effects of DMSO on CsA pharmacokinetics cannot be excluded. Complete pharmacokinetic and immunosuppression studies in

humans are warranted as the use of DMSO as the vehicle for CsA could result in considerable cost savings, provided immunosuppression is not compromised (See e.g., pages 394 and 395).

Further, the secondary reference of Broadwell et al describes the morphologic effect of DMSO on blood-brain barrier. Although, the use of DMSO in the treatment of cerebral infarction, brain swelling, and spinal cord injury is controversial, however, morphological changes were observed on gross or microscopic in brain parenchyma from mice exposed to DMSO concentration of up to 15%. Brains and pituitaries from animals given 0.5 ml of DMSO intraperitoneally and 0.25 ml of DMSO intravenously at concentrations up to 15% did not exhibit hemorrhage. Regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross examination at autopsy. The reference of Broadwell et al concludes by stating that the search of a safe and reliable approach for promoting the entry to the brain of blood-borne chemotherapeutic agents and antibiotics may depend on an increased understanding of the mechanism of blood-brain barrier function. Whether or not DMSO can safely and effectively open the blood-brain barrier *in vivo* to chemotherapeutic drugs and antibiotics requires further investigation. Thus, in view of the above, the reference clearly motivates one of ordinary skill in the art at the time the invention was made to use DMSO as a carrier in any drug of choice because as stated above regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross

examination at autopsy (See e.g., pages 164 and 165). Furthermore, the reference of Elias discloses pharmaceutical compositions comprising cyclosporin wherein the cyclosporin is CsA having a concentration from 0.1 to 50% of a cyclosporin based on total weight and useful for topical application (See e.g., col. 9, line 36-37 and claims 1 and 2). Thus, the secondary references clearly show the use of DMSO as a carrier/penetrating agent in a medicinal formulation wherein the medicinal agent or formulation could be the combination of DMSO and any agent of interest, which may include cyclosporins, particularly CsA at claimed concentrations.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of the primary reference of Kaswan or the reference of Elzinga et al with the reference of Broadwell et al or Elias in order to administer cyclosporin and DMSO by any one of the modes of administration recited in claims 3-6 and 10. The artisan of ordinary skill in the art utilizing the methods of Broadwell et al would have obtained the improvement when such combinations and formulations (as disclosed in the primary reference) are administered to patients suffering from the diseases or conditions recited in claims 11 and 12. Further, such features (i.e., using DMSO as a carrier on blood-brain barrier) are known or suggested in the art, as seen in the secondary reference, and including such features into the composition of the primary reference of '047 patent would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claims 8 and 9, an article of manufacture comprising packaging material and pharmaceutical agent or formulation claimed for the intended purposes for reducing or treating neuronal damage and for causing immunosuppression when administered; but, where the above reference differs from claims 8 and 9 in not teaching *per se* the formulation claimed in a packaging material and use thereof. However, it would have been obvious to package the composition required for the method into packaging material and/or kit format of the well-known commercial expediency of dong so. Therefore, in view of the above, in view of the combined teachings of the prior art, and in the absence of unexpected results or factual evidence to the contrary, modifications such as the selection of an appropriate cyclosporin and formulations of packaging material and/or kit thereof, would have resulted in the claimed invention which was *prima facie* obvious to make and use at the time it was made.

CONCLUSION AND FUTURE CORRESPONDANCE

6. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CAMPELL BRUCE can be reached on (571) 272 0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
November 1, 2005